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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/654,293      | 09/01/2000  | Leandro Christmann   | 22491.0005          | 5636             |

25213 7590 02/17/2004

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EXAMINER

TON, THAIAN N

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1632

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|  |                                      |  |  |
|--|--------------------------------------|--|--|
| <p align="center"><b>Office Action Summary</b></p> | <b>Application No.</b><br>09/654,293 | <b>Applicant(s)</b><br>CHRISTMANN ET AL. |  |
|  | <b>Examiner</b><br>Thai-An N Ton     | <b>Art Unit</b><br>1632                  |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 31 October 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6, 14-22, 24, 32 and 33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 14-22, 24, 32-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) ☐ All   b) ☐ Some \*   c) ☐ None of:  
     1. ☐ Certified copies of the priority documents have been received.  
     2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
     3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
 a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

### DETAILED ACTION

Applicants' Amendment, filed 10/31/03, has been entered. Claims 1, 14, 19, 22 and 24 have been amended. Claims 1-6, 14-22, 24 and 32-33 are pending and under current examination.

Any rejection made of record in the prior Office action and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-6, 14-22, 24 and 32-33 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is *maintained* for reasons of record.

Applicants request clarification as to why independent claims 32-33 have been included in the instant rejection under 112, 1<sup>st</sup> ¶, as the claims refer to methods of preparing recipient cells. See p. 8, last ¶ of the Response.

Claims 32-33 have been included in the prior rejection because the only contemplated use for the recipient cell, as claimed, is for NT methods; and as stated in the prior Office actions, the NT methods contemplated by the specification are not enabling for reasons of record.

Applicants traverse the argument set forth in the prior Office action, particularly, that the Examiner maintains that the nuclear transfer (NT) art is unpredictable. Applicants argue that independent claim 1, as now amended, specifies that the reconstructed zygote or oocyte is transferred into an oviduct of a female recipient of the same species and is allowed to develop to term such that a hard shell egg is laid by the female. This egg is then incubated in order to hatch the transgenic chicken. Applicants argue that this amendment renders the claims in condition for allowance. See pp. 7-8 of the Response. Applicants argue that they have provided an enabled use for the claimed chicken zygote or oocyte, and that a step-by-step procedure of how the reconstructed zygote/oocyte can be transferred into a recipient hen to produce a transgenic chicken.

Applicants' arguments are not found to be persuasive. The contemplated use of the chicken zygote or oocyte is to produce a transgenic chicken; however, the state of the art of nuclear transfer is such that one could not predictably produce a transgenic cloned chicken without undue experimentation, as stated in the prior Office actions. As such, the contemplated use of the chicken zygote/oocyte is not enabling because neither the instant specification nor the state of the art provide

sufficient guidance or teachings with regard to the production of NT-generated transgenic chickens. Applicants further argue that the Tanaka reference, which is incorporated by reference in the instant specification, teaches chicks produced by IVF by returning the fertilized ovum into the oviduct of recipient hens to complete the egg shell formation, and that Tanaka successfully hatched 6 live chicks from 12 fertile ova, and 9 healthy chicks from 10 control ova. Thus, Applicants conclude that in 1994, fertile eggs can be obtained through IVF of ova removed shortly after ovulation and subsequently transplanted into the oviduct of recipient hens. See pp. 9-10, bridging ¶ of the Response. This argument is not found to be persuasive. Tanaka's teaching is directed to IVF, which is not an analogous procedure to NT. IVF procedures do not require the enucleation of a recipient oocyte, the transfer of nuclear material into the recipient oocyte, and the activation of the resulting NT unit, which then is required to further develop to form a fully developed animal. IVF is a procedure of fertilization that is *ex vivo*, and has none of the art-recognized unpredictabilities of the NT art. Westhusin [cited in the prior Office actions] state that unpredictable factors to consider in NT include the species, acquisition of mature ova, enucleation of mature ova, nuclear transfer into the enucleated ova, activating the NT unit, culturing the embryo *in vitro* and transferring the embryo into a surrogate mother. Campbell [J. of Anat., 200:26-275 (2002)] contrast between fertilization and nuclear transfer [see pp. 267], stating that in NT, "No fertilization occurs and therefore there is neither maternal nor paternal DNA present in the

resulting zygote. In normal sexual reproduction the egg and the sperm are not equal contributors; although both contribute genetic information, the egg contains numerous other factors essential for development.” See pp. 267-267, bridging ¶. Campbell further state that, “The only true measure of the efficiency of the NT process is the production of viable offspring. The development of reconstructed embryos is influenced by many factors, including the quality of the recipient oocyte, method of activation and culture methods. Similarly, induction and maintenance of pregnancy is dependent upon a range of factors influenced by both the quality of the transferred embryo and the age, seasonality, nutritional and hormonal status of the recipient.” See p. 271, last ¶.

Applicants further point to the specification to support that the instant invention is enabled, by citing Wilmut and Campbell, who report the production of reconstituted animal embryos via NT of a diploid donor cell into a suitable recipient cells, and the generation of live born lambs. See p. 10, 2<sup>nd</sup> ¶. This is not found to be persuasive, as stated previously, that NT as a broad-based art, is not predictable; thus lacking specific guidance by the specification to enable the claimed invention, there would not be a reasonable expectation that NT in chickens, as claimed, would work because part of the unpredictability of the NT process is species specific. Applicants argue that the teachings of the specification provide considerable guidance and direction of how to use the reconstructed zygote or oocyte in order to produce a transgenic/cloned chick, and therefore undue experimentation is not

required. Applicants argue that the Examiner does not provide a specific example of why the quantity of experimentation would be undue when practicing the instant invention other than citing general references with respect to the NT art. Applicants point to Westhusin, who shows the unpredictable state of the art of NT and specifically discuss the cloning of cattle, sheep, goat, mice and pigs, however, they do not specifically discuss the cloning of chickens. Further, with regard to Wall [cited in the prior Office actions], who teaches that the state of the art of transgenesis is unpredictable, there is no specific mention of chickens. Applicants argue that because there is no specific discussion of NT in chickens on the part of the Examiner, and that Applicants have provided teachings with regard to the generation of transgenic chickens via germline transfer, and to the production of cloned sheep, this challenges the idea that NT is inherently unpredictable. Applicants argue that, "In fact, if that were the case it would not have been possible to ever produce such advanced species as sheep via NT." See pp. 11-12 of the Response.

Applicants' arguments are not found to be persuasive. Although the art is silent with regard to the generation of transgenic chickens produced by NT, this does not provide evidence for the unpredictability or predictability of such a method. Westhusin clearly teach that the methods and protocol for cloning of other animals by NT is not predictable, and that each will technique varies from species to species. See pp. 36-37, bridging ¶. It is further noted that the NT art cited by both the

Examiner and Applicants are directed to mammalian species, which reproduce differently from avian species. Although protocols have been developed in particular mammalian species [e.g., cattle, sheep, etc.], these protocols are species-specific, which support the unpredictability of the NT art. Pennisi and Vogel [Science, 288:1722-1727] review the unpredictabilities in generating cloned mammalian animals. They quote Wall who states that, "Despite years of effort, "we're still in the same bind that we've always been in. A majority of [would-be-clones] do not make it to term." See p. 1722, 1<sup>st</sup> column, 2<sup>nd</sup> ¶. Wilmut states that, "[E]normous hurdles must be overcome before cloning becomes practical, much less profitable. First and foremost is the problem of efficiency, which remains at a less-than-impressive 2%; out of some 100 attempts to clone an animal, typically just two or three live offspring result. Even when an embryo does successfully implant in the womb, pregnancies often end in miscarriage. A significant fraction of the animals that are born die shortly after birth. And some of those that survive have serious developmental abnormalities, suggesting that something in the recipe is fundamentally wrong." See p. 1722, col. 1-2, bridging ¶. With regard to the cloning of various species, they state that, "In all species, the basic hurdles are the same, but the details differ sufficiently that each species has gotten sidetracked at different points along the way to becoming a commercially or medically useful clone." See p. 1722, 3<sup>rd</sup> col., 2<sup>nd</sup> ¶. Pennisi and Vogel teach that with regard to the cloning of cattle from an adult or fetal cell, the basic methodology of NT had to be



altered [by Wilmut and Campbell] to synchronize the cell-division cycle of donor cells to that of the egg. Further, it is noted that one of the major obstacles in NT is the high number of problematic pregnancies and abnormal fetuses. The mere production of a live born offspring by NT fails to ensure its normalcy, many NT-produced offspring are larger than normal, and many fail to live, or die shortly after birth. See p. 1724. Pennisi and Vogel further state that the efficiency and predictability of NT varies from species to species. For example, goats appear to be easier to clone than rabbits or mice. Further, with regard to NT in chickens, they state that methodologies are still being developed. See p. 1725, col. 2-3. The instant specification fails to provide sufficient teachings or guidance to overcome the unpredictability with regard to the generation of chickens via NT. In particular, the specification fails to provide specific teachings with regard to the transfer of a reconstructed chicken zygote/oocyte into the oviduct of a recipient female, the laying and incubating of the resulting egg and the generation of a transgenic, cloned chicken, and one of skill would not be able to rely upon the state of the art of NT to produce such chickens, as the art clearly shows that NT methods are species-specific.

Applicants further point to the various US Patents which are incorporated by reference in the instant specification, which teach how a nuclear donor cell is transfected with a vector construct. Applicants argue that, for example, Bosselman produced transgenic chickens whose cells contained and expressed an replication-

defective retroviral vector nucleic acid sequence, and thus, the prior art and Applicants' teachings provide considerable direction and guidance of how to produce the transgenic/cloned chick as claimed. See p. 10 of the response. This is not found to be persuasive because the claims not only require that the resulting chicken be transgenic, but produced from a NT procedure, which is unpredictable [see *supra*]. Transgenesis, as a broad-based art, is found to be unpredictable because of unpredictabilities such as the random integration of the transgene construct [see Wall, cited in the prior Office actions]. Furthermore, although Bosselman teach the production of transgenic with a particular vector, it is reiterated that the expression of the transgene and the effect of the transgene expression depends upon the particular gene construct used. Applicants have failed to provide teachings or guidance to overcome the art-recognized unpredictabilities associated with the transgenics art.

Therefore, in view of the quantity of experimentation necessary to determine the parameters for nuclear transfer for the production of reconstructed chicken zygotes, oocytes or cloned or transgenic chickens, the lack of direction or working examples provided by the specification for the production of cloned or transgenic chickens, as well as the unpredictable state of the art of nuclear transfer and transgenics, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

***Claim Rejections - 35 USC § 112***

The prior rejection of claims 1-6, 14-22, 24 and 32-33 is withdrawn in view of Applicants' amendments to the claims.

***Claim Rejections - 35 USC § 102***

The prior rejection of claims 25 and 26 under 35 U.S.C. §102 is rendered moot in view of Applicants' cancellation of the claims.

*Conclusion*

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (571) 272-0548. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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